REMARKS

The May 12, 2009 Official Action has been carefully considered. In view of the amendment submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the May 12, 2009 Official Action. The initial due date for response, therefore, was August 12, 2009. A petition for a three (3) month extension of the response period is included with this amendment and request for reconsideration, which is being filed before the expiration of the three (3) month extension period.

As another preliminary matter, it is noted that the restriction requirement set forth in the preceding Official Action has been maintained and made final. Applicants again reiterate that their election of the Group II claims, i.e., claims 22-32, 36-41 and 51 in response to the aforementioned restriction requirement is without prejudice to their right to file one or more divisional applications, as provided in 35 USC §121, directed to any subject matter held finally withdrawn from consideration in this application.

Turning to the substantive aspects of the May 12, Official Action, the Examiner has objected to claims 22 and 55 for containing certain minor informalities. These claims have been amended in keeping with the Examiner's suggestions, thereby rendering these objections moot.

At page 5 of the Official Action, the Examiner has rejected claims 22, 23, 26, 27, 32, 36, 38, 39, 41 and 42 under 35 U.S.C. §112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The rejection of claims 22, 23, 26, 27, 32, 36, 38, 39, 41 and 42 has been maintained for allegedly failing to comply with the written description and enablement requirements of 35 U.S.C §112, first paragraph.

The Examiner has rejected claims 22, 26, 32, 36, 38, 39, and 55 under 35 USC §103(a) as allegedly unpatentable over the combined ***13*** disclosures of Meijer et al., Chijiwa et al., Lau et al., Castro et al, Singh et al., and Kuret in view of Graves, Vitek, Hasegawa et al., Curran et al., Hanger et al., Morishima-Kawashima et al., and Anderton et al.

Claims 23 and 27 also stand rejected under 35 USC §103(a) as allegedly unpatentable over the same ***thirteen (13)*** references, and further in view Ford et al.

Claims 41-42 stand further rejected under 35 USC §103(a) as allegedly unpatentable over the same ***thirteen (13)*** references set forth above and further in view of Zhu et al.

Claims 22, 26, 32, 36, 38, 39, 41, 42, and 55 stand rejected under the judicially created doctrine of obviousness type double patenting.

The foregoing objections and rejections constitute all of the grounds set forth in the May 12, 2009 Official Action for refusing the present application. Each of the aforementioned rejections is respectfully traversed for the reasons set forth below.

SUMMARY OF THE TELEPHONIC INTERVIEW

Applicants, through their undersigned attorneys, requested a telephone interview with Examiner Steadman, which was held 13 July 2009. The courtesy extended to applicants' attorneys in granting the interview is appreciated. The purpose of the interview was to discuss a proposed amendment of claim 22 with Examiner Steadman, and in particular to point out the reasons why the amended version of claim 22 is believed to comply with the recently promulgated PTO Written Description Training Materials.

Applicants also reiterated that with respect to all of the prior art rejections and obviousness-type double patenting rejections, that many of the tau protein phosphorylation sites recited in the pending claims were unknown prior to the present invention. Notably the claim has been amended to require detection of these novel phosphorylation sites, rather than all and any phosphorylation sites on tau that may or may not be associated with disease.

Limiting the method of claim 22 to require 95% identity to the recited reference SEQ ID NOS: was proposed in order to address the Examiner's concerns regarding the alleged lack of adequate written description and enablement. Applicants indicated that the three dimensional structures of the recited proteins were known in the art. Accordingly, the skilled person would have guidance as to where variant amino acids could be tested. Moreover, such variation must fall within the 95% identity requirement and result in a protein that retains CK1 activity, e.g., phorphorylation of tau, or in the case of tau protein variants, remain a substrate for CKI phosphorylation. The natural allelic variation in the genetic code was also discussed. Applicants also noted that the effect of limiting the claims to the recited sequences only would dramatically impede Applicant's recourse should the claims be infringed by a competitor who employs slightly different sequences for CKI and tau.

At the conclusion of the interview, Examiner Steadman indicated that further consideration would be required to determine whether the proposed claim amendments would overcome the written description, scope of enablement, obviousness and obviousness-type double patenting rejections in the Official Action outstanding.

THE METES AND BOUNDS OF CLAIMS 22,23, 26, 27, 32, 36, 38, 39, 41 AND 42 AS AMENDED ARE CLEAR TO ONE OF SKILL IN THE ART

The Examiner has rejected claim 22 and claims dependent therefrom as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Specifically, the Examiner contends that the claimed method does not require that the tau protein have any of the recited phosphorylatable residues and that the claim lacks clarity as drafted. While not agreeing with the Examiner's contention, claim 22 has been amended to remove any perceived ambiguity. Specifically, the phrase "is capable of" has been removed. The phraseology relating to the SEQ ID NOS has been removed and variant CK1 and tau proteins are required to have greater than 95% identity to the reference sequence. The amendments to claim 22 are fully supported by the application as filed and obviate the rejection of the aforementioned claims under 35 U.S.C. §112, second paragraph. Accordingly, the rejection should be withdrawn.

CLAIMS 22, 23, 26, 27, 32, 36, 38, 39, 41 AND 42 AS AMENDED FULLY SATISFY THE WRITTEN DESCRIPTION AND ENABLEMENT REQUIREMENTS OF THE PATENT STATUTE

A. Written Description

It is the Examiner's position that the aforementioned claims fail to satisfy the written description requirement under 35 U.S.C §112, first paragraph. Specifically, the Examiner asserts that the specification fails to provide an adequate written description to reasonably convey that the Applicants had possession of the invention since the genus of CK1 and tau proteins have not been described by specific structural features. Applicants respectfully disagree.

It is without question that the skilled artisan having the present specification before him would fully appreciate that the present inventors were in possession of a screening method for

identifying agents which inhibit CK1 phosphorylation of tau at specifically recited sites on tau protein. Claim 22 has been amended to include variants of SEQ ID NOS 1 and 2 having at least 95% identity to the reference sequences. Support for this amendment can be found at page 17, line 28. As the Examiner acknowledges, CK1 has been isolated from humans, yeast, bovines and rats and thus sequence variation for this protein is known in the art. Moreover, the three dimensional structure of this molecule is known. See for example, Longenecker et al. J. Mol. Biol. (1996) 257:618-631; Machhoon et al., J. Biol. Chem. (2000) 275:20052-60. The availability of the sequence information as well as the crystal structure of the protein provides the skilled artisan with the necessary guidance as to where amino acid variation could be tolerated. This information which was in the public domain as of Applicants filing date, provides a full written description of CK1 variants having at least 95% identity with the reference sequence and the skilled artisan could readily identify and employ such variants in the method of claim 22 as amended. Indeed, as set forth in the written description guidelines promulgated by the USPTO on March 25, 2008, "with the aid of a computer, one of skill in the art could have identified all of the nucleic acids that encode a polypeptide with at least 85% sequence identity with SEQ ID NO: 2. Thus, one of ordinary skill in the art would conclude that applicants were in possession of the claimed genus at the time the application was filed."

The Examiner is reminded that subject matter which is known in the art is preferably omitted from a patent disclosure. Inasmuch as the CK1 sequence, and homologues thereof and the CK1 three dimensional structure were known in the art, Applicants submit that those skilled in this art area would have no doubt whatsoever that the inventors had possession of screening method encompassed by claim 22 as amended and claims dependent therefrom. Furthermore, limiting the claims to variants having at least 95% identity with the reference sequence significantly limits the number of protein variants encompassed by the claim. Moreover, inoperable sequences would be outside the scope of the present claims.

Applicants reiterate that it would be inequitable for the USPTO to insist upon the limitation of the claims to only one sequence. As stated in In re Goffe, 191 USPQ 429 (CCPA 1976, "For all practical purposes, the Board would limit Appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors."

The Examiner also contends that Applicants do not identify essential regions of CK1protein and tau protein encoded by the reference SEQ ID NOS:. This assertion is erroneous on its face. As mentioned above, the three dimensional structures of the CK1 protein as well as the active phosphorylation site was known in the art at the time the application for patent was filed. Thus, essential regions of this protein are known. Tau protein structure had also been well characterized as of Applicants filing date. See Li et al. J. Biol. Chem. (2002) 277:41390-41400; Lee et al. J. Cell Biol. (1989) 109: 1643–1651. Applicants also contend that provision of specific amino acid residues in tau that are targets for phosphorylation provide essential regions of this protein. However, even if these structures were not known, the Examiner's attention is respectfully drawn to the recent Federal Circuit decision Falkner v. Inglis, where the Court held that "there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Thus, the Examiner's requirement appears to be misplaced and contrary to recent case law.

As set forth in *Ex Parte Cole,* 223 USPQ 94, 95 (31 May 1983) "Claims are addressed to the person of average skill in the particular art. Compliance with §112 must be adjudged from that perspective, not in a vacuum. It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination". As mentioned above, the CKI and tau variants encompassed by the claims must have at least 95% sequence identity with the proteins encoded by the reference sequence. This feature, coupled with the disclosure in the specification, and the publically available structural information fully satisfies the written description requirements of the statute. Inasmuch as the skilled person would conclude that applicants were in possession of the invention encompassed by claim 22 as amended, it is submitted that the rejection of this claim and claims 23, 26, 27, 32, 36, 38, 39, 41 and 42 for inadequate written description is inappropriate and should be withdrawn.

B. Enablement

The claims as amended are directed to a screening method for identifying agents which inhibit CK1 phosphorylation of tau on one or more specifically recited amino acid residues and the specification as filed fully enables practice of the instantly claimed method. Notably, the

examiner acknowledges at page 10 of the October 3 Official Action that the present specification is "enabling for methods using art-recognized CK1 and tau proteins". These would include, at least, human CK1α, β, γ, δ forms, both natural and recombinantly expressed (see Graves), bovine brain and kidney CK1 and yeast CK1 (see Singh) as the CK1 variants, and bovine (see Singh), murine (see the '084 patent to Anderton and Miller) and human tau (see Lau) as tau protein variants.

Applicants note that claim 22 has been amended to recite CK1 or CK1 variants having 95% sequence identity therewith "which phosphorylate tau at one or more sites recited in the Markush group in step a). Accordingly, CK1 or the variant thereof must phosphorylate tau at one or more of the specified sites and the tau variant must comprise one or more of the specified sites. In view of the amendment to claim 22, it is clear that the skilled person can readily practice the method of claim 22 and claims dependent therefrom without resorting to undue experimentation.

The quantity of experimentation needed to determine the feasibility of using the full scope of CK1 and tau protein variants, as presently claimed in applicants' screening method, cannot be considered extensive given the new requirement for 95% sequence identity with the reference sequences. As set forth in the written guidelines, such variant sequences are readily generated by the skilled person using any of a number of appropriate computer programs. Notably, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). To the same effect is *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (ITC 1983), *aff'd. sub. nom, Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985), in which it was observed that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

For all of the above reasons, the rejection of claims 22-29, 32, 36, 38, 39, 40 and 42 as amended for allegedly failing to satisfy the enablement requirement of 35 USC §112, first paragraph, is improper and should be withdrawn upon reconsideration.

CLAIMS 22, 26, 32, 36, 38, 39, AND 55 AS AMENDED ARE PATENTABLE OVER THE PRIOR ART CITED BY THE EXAMINER

At page 12 of the Official Action, the Examiner has asserted that the aforementioned claims are not patentable over the combined disclosure of **13 references**, namely Meijer et al., Chijiwa et al., Lau et al., Castro et al, Singh et al., and Kuret in view of Graves, Vitek, Hasegawa et al., Curran et al., Hanger et al., Morishima-Kawashima et al., and Anderton et al. The deficiencies of these references have been made of record and were discussed at length in Applicants previous response. At page 13, the Examiner provides his interpretation of the scope of claim 22 and asserts that the term "identifying" has been construed as "looking for" or "seeking to know" the sites of tau phosphorylation by CK1 without *a priori* knowledge of such sites". Applicants submit that in view of the amendment to claim 22, this interpretation is no longer appropriate. Indeed, claim 22 as amended specifically identifies a select number of sites rather than "any and all phosphorylation sites" present on the tau protein and requires that CK1 or a variant thereof phosphorylate tau at one or more of these sites. As stated in applicants previous responses, many of these sites were unknown as of applicant's filing date. The Examiner is reminded that it is a well settled premise in patent law, that silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow". In re Burt, 148 U.S.P.Q. 548 (CCPA 1966).

Citing references which merely indicate that isolated elements in the claims are known is not a sufficient basis for concluding that the combination of claimed elements would have been *prima facie* obvious. *Ex parte Hiyamizu,* 10 USPQ 1393, 1394 (PTO BPAI 1988). To the same effect is *Ex parte Levengood,* 28 USPQ 1300 (PTO BPAI 1993) (examiner cannot establish obviousness by locating references which describe various aspects of applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what applicant has done). Here, as in *Levengood,* the references cited as evidence of obviousness "fall short of providing the 'motivation' or 'suggestion' to assemble their teachings into a viable process". *Id.* at 1302.

It is submitted that the thirteen references relied on by the Examiner fail to place each and every element of the method of claim 22 as amended in the hands of the public. Accordingly, a prima facie case of obviousness has not been established and thus the rejection of claims 22, 26,

32, 36, 38, 39, and 55 on this ground is untenable and should be withdrawn.

At page 17 of the Official Action, the Examiner rejects claims 23 and 27 under 35 U.S.C. §103(a) as allegedly obvious over the 13 references relied on above and further in view of Ford et al. The Examiner contends that Ford et al. teach the use of affinity tags to purify recombinant proteins. Notably, in this instance the Examiner is reading limitations into the claims that are not present. Additionally, Applicants are confounded by the conflicting positions taken in this official action. How can the Examiner assert that the variants encompassed by claims 23 and 27 are inadequately described in the specification (see ¶15 of the Action) and yet at the same time assert that the use of such variants is obvious over art that does not teach the variant sequences. The Examiner cannot have it both ways. In response, Applicants submit that the combination of the 13 references relied on by the Examiner fail to place the invention in the hands of the public and the addition of Ford et al. to this rejection does not rectify this deficiency. Accordingly, the rejection of claims 23 and 27 as allegedly unpatentable over the prior art cannot be maintained and should be withdrawn.

At ¶19, the Examiner has rejected claims 41 and 42 over the same 13 references cited above and has added Zhu et al. Zhu et al. is relied upon for teaching protein chips for protein kinase assays. In response, Applicants submit that Zhu et al. is generally concerned with assaying kinase activity and not assays involving identification of substances which specifically inhibit CK1 phosphorlyation of tau at predetermined, previously unknown sites. As mentioned previously, this feature of the claim cannot be found in the combined prior art relied on by the Examiner. Accordingly, the rejection of claims 41 and 42 as amended is untenable and should be withdrawn.

Applicants have developed a method to more accurately predict therapeutically efficacious inhibitors of CK1. The problem was solved, in accordance with the present invention, through the provision of a number of previously undescribed phosphorylation sites in tau protein that are found in pathological forms of PHF tau, but which are not found to be phosphorylated in normal tau, and means for quantifying the level of phosphorylation at each site. The sites set forth in the amended claims were not described or suggested in the prior art. See, in particular, claims 32 and 55.

The conclusion is inescapable, therefore, that applicants' improved method of identifying specific inhibitors of CK1-mediated phosphorylation at specific sites on tau protein is patentably

distinguishable over the references of record.

CLAIMS 22, 26, 32, 36, 38, 39, 41 and 42 AND 55 ARE PATENTABLY DISTINCT OVER CLAIMS 6-9 AND 12 OF US PATENT 5,994,084 TO ANDERTON ET AL.

Obviousness-type double patenting is a judge-made doctrine based on public policy, which has as its objective the prevention of unjustified or improper time-wise extension of the right to exclude conferred by a U.S. patent. This policy is effectuated by refusing issuance of separate patents on applications that claim obvious variations of the same invention. In this case, however, there is no possibility for unjustified or improper time-wise extension of applicants' patent rights because the present claims cannot possibly constitute an obviousness variation of the method for testing therapeutic agents for treating Alzheimer's disease claimed in claims 6-9 and 12 of the '084 patent.

The impropriety of the present rejection has been addressed at length in applicant's previous response. Applicants reiterate the Examiner's broad interpretation of claim 22 is no longer accurate given the amendments presented herein. In contrast to the Examiner's stated position, the claim does not read on "necessarily analyzing any and all sites of phosphorylation of tau". It is clear that the disclosure in the '084 patent fails to place the method of claim 22 as amended in the public domain and nor would the skilled person having the '084 disclosure before him or her arrive at the subject matter instantly claimed. In view of these clear differences between the present claims as amended and the claims in the '084 patent, the grant of a patent on the present application could not conceivably result in a time-wise extension of the '084 patent grant. Thus the rejections on this ground should be withdrawn.

CONCLUSION

It is respectfully requested that the amendments presented herewith be entered in this application, since the amendments are primarily formal, rather than substantive in nature. This amendment is believed to clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case.

In view of the amendments presented herewith, and the foregoing remarks, it is respectfully urged that the rejections set forth in the May 12, 2009 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone or in-person interview, the Examiner is requested to call the undersigned at the phone number given below.

Respectfully submitted,
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